CLINICAL TOXICOLOGY

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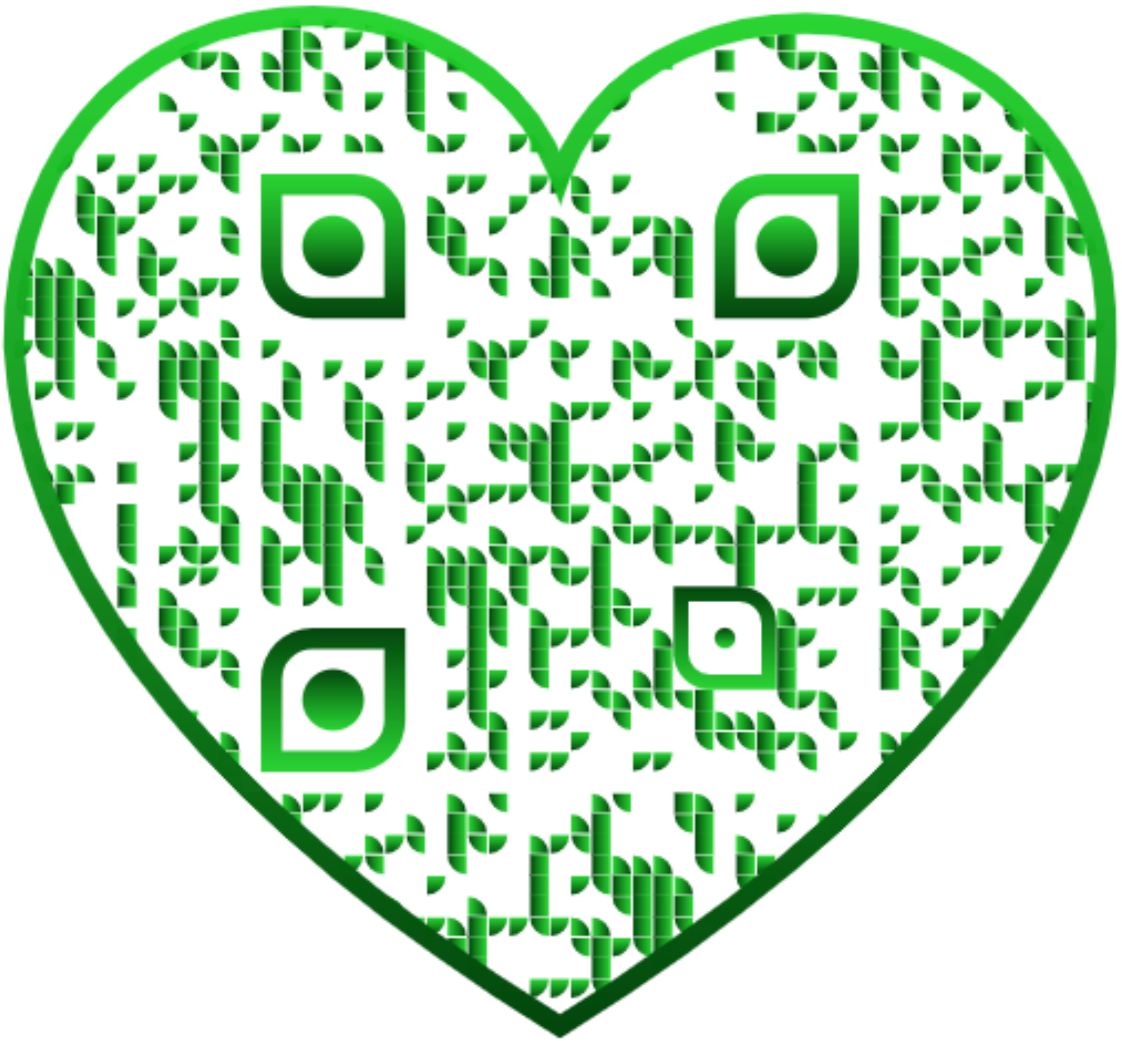


Learning Objectives

- Toxicological events as a result of
  - » Therapeutic drug administration
  - » Inadvertent drug exposure
  - » Deliberate exposure to drugs
- Toxicokinetics and Toxic mechanisms of drugs
- Detection, identification and clinical management of drug/TOXICANT poisoning
  - » Specific antidotes
  - » Supportive therapeutic management
- Signs and symptoms of syndromes due to drug poisoning

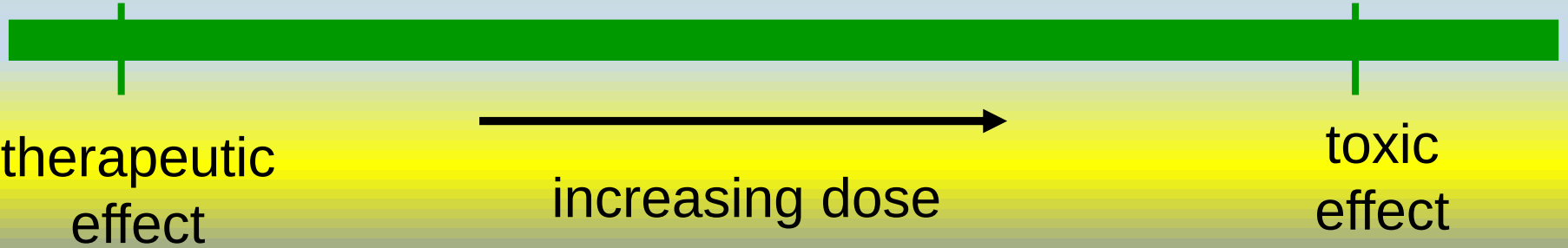
Clinical Toxicology

- **Definition**
  - The discipline (within toxicology) concerned with the toxic effect of agents whose intent is to treat, ameliorate, modify, or prevent disease states
  - Also include agents used with non-therapeutic intent, for example, alcohol and drugs of abuse
  - It is concerned with disease caused by or uniquely associated with toxic substances (e.g. poison management)

Paracelsus (1493-1541)
'Grandfather of Toxicology'

"***All things are poison and nothing is without poison, only the dose permits something not to be poisonous."***

"**The dose makes the poison**"



PREVENTION & TREATMENT OF POISONING

- Treatment of acute poisoning must be prompt.
- Goals of treatment
  - To maintain the vital functions if their impairment is imminent
  - To keep the concentration of poison in the crucial tissues as low as possible by
    - preventing absorption
    - enhancing elimination
  - To combat the pharmacological and toxicological effects at the effector sites

Clinical Management of Toxicologic Emergencies

Involves a stepwise approach

1. Stabilization of the patient
2. Clinical evaluation (history, physical examination, and laboratory and/or radiological tests)
3. Prevention of further absorption, exposure, or distribution
4. Enhancement of elimination of the suspected toxin
5. Administration of an antidote
6. Supportive care and follow-up

Stabilization of the patient

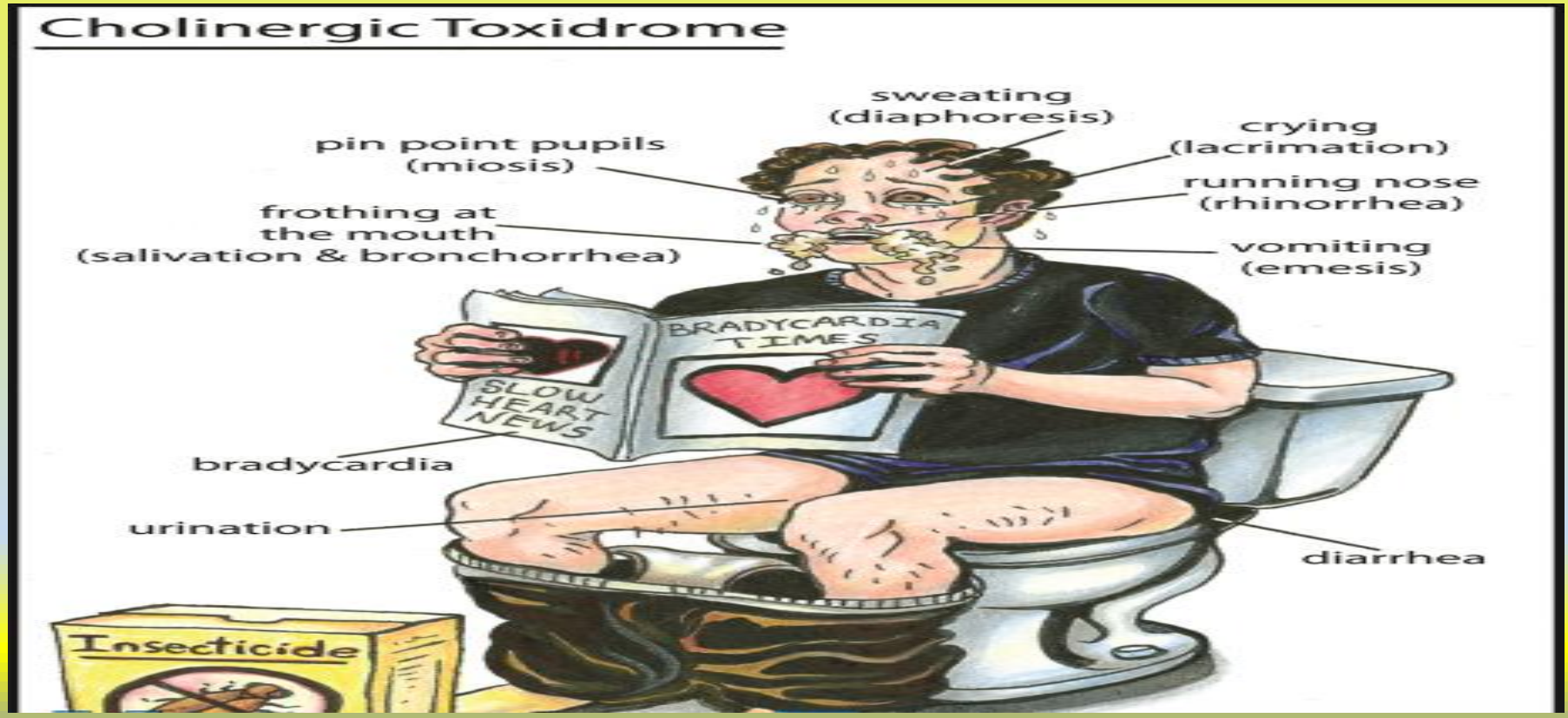
- Involves:
  - General assessment of the situation & the environment
  - Overall appearance of the patient
  - Maintenance of vital signs
- Removal of the victim from the obvious source of contamination, such as from fumes, gas, or spilled liquid.
- Maintenance of the **ABCs** of clinical management

("**ABCDs**" of poisoning treatment)

- **A**irway
- **B**reathing:Airway clearance, O2 saturation, RR and Depth of Breathing
- **C**irculation:Pulse, Heart Rate and regularity, Blood Pressure
- **D**isability
- **D**on't **E**ver **F**orget the **G**lucose
- **E**xposure
- **G**et a set of basic observations

TOXIDROMES

A toxidrome comprises a constellation of clinical signs and symptoms that, taken together, are likely associated with exposure from certain classes of toxicologic agents.



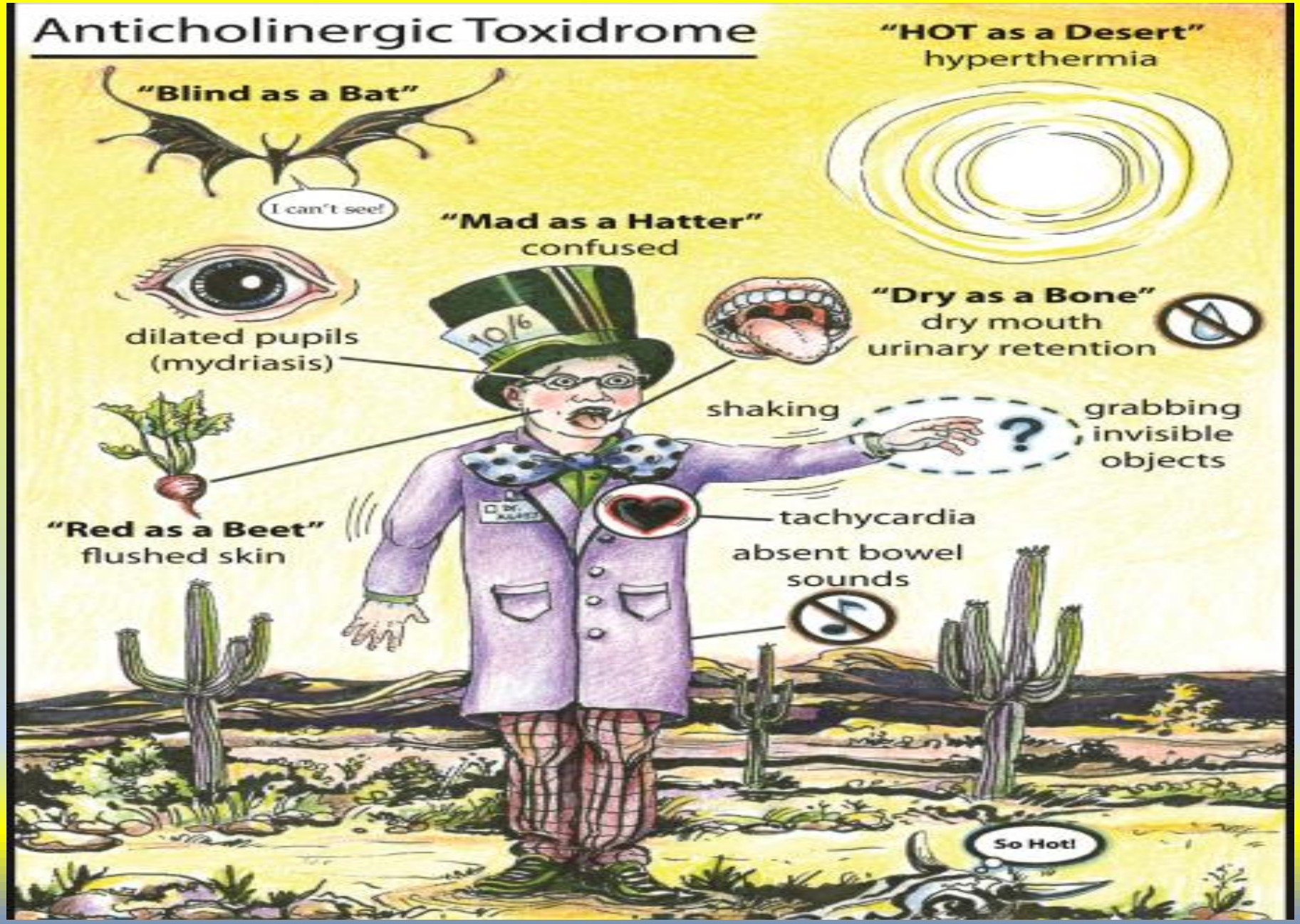

Anticholinergic Toxidrome
"Blind as a Bat"
I can't see!
"HOT as a Desert"
hyperthermia
"Mad as a Hatter"
confused
dilated pupils
(mydriasis)
"Dry as a Bone"
dry mouth
urinary retention
shaking
grabbing
invisible
objects
"Red as a Beet"
flushed skin
tachycardia
absent bowel
sounds
So Hot!

TABLE 3.5
Common Toxidromes and Their Clinical Features

Anticholinergic	Dry mucous membranes, flushed skin, urinary retention, decreased bowel sounds, altered mental status, dilated pupils, cycloplegia
Sympathomimetic	Psychomotor and physical agitation, hypertension, tachycardia, hyperpyrexia, diaphoresis, dilated pupils, tremors; seizures (if severe)
Cholinergic	SLUDGE (sialorrhea, lacrimation, urination, diaphoresis, gastric emptying), BBB (bradycardia, bronchorrhea, brochospasms); muscle weakness, intractable seizures
Opioid	CNS depression, miosis, respiratory depression, bradycardia, hypotension, coma
Benzodiazepine	Mild sedation, unresponsive or comatose with stable vital signs; transient hypotension, respiratory depression

Clinical evaluation

- Documentation of history of events leading to emergency
  - Determination of substance ingested
  - Time of exposure
- Physical examination: identification of clinical signs and symptoms that, together, are likely associated with exposure from certain classes of toxic agents.
  - The identification of the toxic syndrome or "toxidrome," this compilation of observations allows for the initiation of treatment & progress toward follow-up care & support

History & Physical Examination

- **History**
- Fact finding mission – patient, family, friends, GP, empty packets, vomit, anyone !!??
- What ?
- When ?
- How ?
- How much ? (mg / kg)
- What else ? (Including alcohol)
- Why ?

(to determine substance ingested or to know the time and extent of exposure)

- **Physical examination**
  - vital signs
  - eyes and mouth
  - skin
  - abdomen
  - nervous system
- **Vital Signs**
  - BP, pulse, respirations, and temperature
- **Hypertension & tachycardia**: amphetamines, cocaine, & anticholinergics
- **Hypotension & bardycardia**: CCBs, β blockers, & sedative hypnotics
- **Hypotension with tachycardia**: TCAs, vasodilators, & β agonists

- **Rapid respirations**: salicylates, CO, & other toxins that produce metabolic acidosis or cellular asphyxia
- **Hyperthermia**: sympathomimetics, anticholinergics, salicylates & drugs producing seizures/muscular rigidity
- **Hypothermia**: CNS-depressants, esp. when accompanied by exposure to a cold environment
- **Eyes**
  - **Miosis** : opioids, phenothiazines, & AchEIs (eg, organophosphates)& deep coma due to sedatives.
  - **Mydriasis** : amphetamines, cocaine, LSD & anticholinergics.
  - **Horizontal nystagmus**: phenytoin, alcohol, barbiturates, & other sedatives.
  - **Presence of both vertical & horizontal nystagmus**: phencyclidine poisoning.

- **Mouth**
  - Signs of burns due to corrosive substances
  - Soot from smoke inhalation
  - Odors of alcohol, HC solvents, or NH_3may be noted.
- **Skin**
  - **Flushed, hot, & dry**: atropine & other antimuscarinics.
  - **Excessive sweating** : organophosphates, nicotine, & sympathomimetics.
  - **Cyanosis**: hypoxemia or by methemoglobinemia.
  - **Icterus**: hepatic necrosis due to acetaminophen or *Amanita phalloides* mushroom poisoning.
- **Abdomen**
  - **Ileus**: antimuscarinic, opioid, & sedatives.
  - **Hyperactive bowel sounds, abdominal cramping, & diarrhea**: organophosphates, Fe, arsenic, theophylline, *A phalloides,* & *A muscaria.*

- **Nervous System**
  - **Nystagmus, dysarthria, and ataxia**: phenytoin, carbamazepine, alcohol, & other sedative intoxication.
  - **Twitching and muscular hyperactivity**: atropine & other anticholinergics, & cocaine & other sympathomimetics.
  - **Muscular rigidity**: haloperidol & other antipsychotics, serotonin syndrome, & by strychnine.
  - **Seizures**: overdose with antidepressants (esp. TCAs & bupropion), cocaine, amphetamines, theophylline, INH & diphenhydramine.
  - **Coma with absent reflexes**: deep coma due to S/H or other CNS depressant intoxication

Laboratory Procedures

- *Initializing emergency measures should not depend on obtaining laboratory results.*
- *Qualitative and quantitative analysis of biological specimens, however, may be necessary for specific drugs, including: acetaminophen, aspirin, digoxin, iron, lead, lithium & theophylline*
- ***Arterial blood gases***
- ***Electrolytes***
- ***Renal function tests***
- ***Serum osmolality***
- ***Electrocardiogram***

Prevention of Further Absorption of Poison (GI Decontamination)

- *Emesis*
  - *Ipecac*
  - *Apomorphine injection*
- *Gastric lavage*
- *Chemical Adsorption*
- *Chemical inactivation*
- *Purgation*

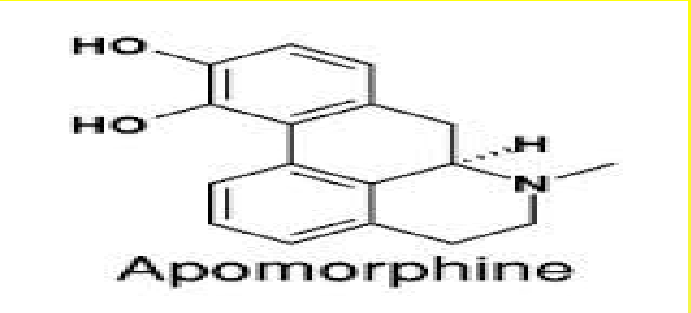
Emesis

- **Contraindicated If the patient:**
  - Ingested a corrosive poison, such as a strong acid or alkali: ↑gastric perforation & further necrosis of the esophagus
  - Comatose or in a state of delirium: aspiration of gastric contents
  - Ingested a CNS stimulant: further stimulation with vomiting may precipitate convulsions
  - Ingested a petroleum distillate (*e.g.*, kerosene, gasoline): regurgitated HCs can cause chemical pneumonitis
- Emesis should be considered if the ingested solution contains potentially dangerous compounds, such as pesticides.

Ipecac

- Has local irritant effect on the enteric tract and its effect on the chemoreceptor trigger zone (CTZ)
- Adminstertaion of ipecac syrup should be followed by a drink of water
- Ipecac can produce toxic effects on the heart because of its content of emetine
- Chronic abuse of ipecac for weight reduction can result in cardiomyopathy, ventricular fibrillation, and death.

Apomorphine



- Stimulates the CTZ and causes emesis.
- Unstable in solution & must be prepared just prior to use & thus is not often readily available.
- Not effective orally & must be given parenteral (SC)
- Can be administered to an uncooperative patient
- Produces vomiting in 3 to 5 minutes.
- Is a respiratory depressant: should not be used in CNS depressant poisoning or if respiration is slow & labored.

- **Rarely used as an emetic. …**

Gastric Lavage

- Inserting a tube into the stomach and washing the stomach with water, normal saline, or one-half normal saline to remove the unabsorbed poison.
- Performed **ASAP**, but only if vital functions are adequate or supportive procedures have been implemented.
- Contraindications similar to emesis, & there is additional potential complication of mechanical injury to the throat, esophagus, & stomach.

- Should be reserved for patients who have ingested a potentially life-threatening amount of poison & when procedure can be undertaken within 60 minutes of ingestion.
- Small volumes (120 to 300 ml) of lavage solution should be instilled into the stomach at one time so that the poison is not pushed into the intestine.
- Lavage is repeated until the returns are clear, which usually requires 10 to 12 washings & a total of 1.5 to 4 L of lavage fluid.

Chemical adsorption

- *Activated charcoal*: adsorbs drugs and chemicals on the surfaces of the charcoal particles
- Many, but not all, chemicals are adsorbed by charcoal.
  - alcohols, HCs, metals, and corrosives are not well adsorbed
- Effectiveness depends on the time since the ingestion and on the dose of charcoal
- Most effective if given in a ratio of at least 10:1 of charcoal to estimated dose of toxin by weight.

Activated charcoal

- Can interrupt enterohepatic circulation of drugs & enhance the net rate of diffusion of the chemical from the body into GIT
- *Activated charcoal* has comparable or greater efficacy, fewer contraindications & complications, & is less aversive & invasive than ipecac or gastric lavage; thus it is the preferred method of GI decontamination in most situations.
- Serial doses of activated charcoal: enhance the elimination of *theophylline* & phenobarbital

Activated charcoal

- Prepared as a mixture of at least 50 g (about 10 tablespoons) in a glass of water.
  - mixture is then administered either orally or *via* a gastric tube.
- Should not be used simultaneously with ipecac: charcoal can adsorb the emetic agent in ipecac
- May adsorb & decrease the effectiveness of specific antidotes.

Chemical Inactivation

- Antidotes change the chemical nature of a poison by rendering it less toxic or preventing its absorption.
  - Formaldehyde poisoning : treated with ammonia to form hexamethylenetetramine
  - Na formaldehyde sulfoxylate: convert mercuric ion to the less soluble metallic mercury
  - $NaHCO_3$ converts ferrous iron to ferrous carbonate, which is poorly absorbed.

Chemical inactivation

- Use of neutralizing agents is controversial because they may produce excessive heat.
- CO_2 gas produced from bicarbonates used to treat oral poisoning with acids can cause gastric distension and even perforation.
- Treatment of choice for ingestion of either acids or alkalis is dilution with water or milk.
- Similarly, burns produced by acid or alkali on the skin should be treated with copious amounts of water.

Purgation

- Rationale: to minimize absorption by hastening passage of toxicant through GIT.
- Cathartics generally are considered harmless unless the poison has injured GIT.
  - indicated after the ingestion of enteric-coated tablets
- *Sorbitol* is the most effective, but *sodium sulfate* and *magnesium sulfate* also are used; all act promptly & usually have minimal toxicity.

Enhanced Elimination of the Poison

- *Whole bowel irrigation*
- *Biotransformation*
- *Urinary excretion*
- *Dialysis*
- *Antagonism / Chemical Inactivation of an absorbed Poison*

Whole bowel irrigation

- Oral administration of polyethylene glycol, at a rate of 2 l/hr, can flush ingested toxic agents through the bowel.
- Administration of the preparation is continued for 4 to 5 h, or until the bowel effluents are clear.
- Useful for enhanced elimination of sustained-released preparation of capsules or tablets, packets of street heroin or cocaine, and agents not effectively adsorbed with charcoal.

Biotransformation

- Metabolism might lead to more toxic chemicals.
- Thus inhibition of biotransformation ↓ toxicity of such drugs.
- ***Ethanol***: inhibit conversion of methanol to its highly toxic metabolite, formic acid, by ADH.
- **Acetaminophen** is converted by the CYP system to a metabolite that is detoxified by GSH
  - Acetaminophen does not cause hepatotoxicity until GSH is depleted
  - Liver can be protected by maintenance of the conc. of GSH, & this can be done by the admn. of *N*-acetylcysteine

Urinary Excretion

- Diuretics facilitate urinary excretion
- *Furosemide* is used most often, but osmotic diuretics also are employed.
- Forced diuresis should be used with caution in patients with renal, cardiac, or pulmonary complications.
- Nonionized compounds are reabsorbed far more rapidly than ionized polar molecules→a shift from the nonionized to the ionized species of the toxicant by alteration of the pH of the tubular fluid may hasten elimination.

Urinary Excretion….

- Acidic cpds such as phenobarbital & salicylates are cleared much more rapidly in alkaline than in acidic urine.
- Urine alkalinization ↑s urine elimination of *chlorpropamide, methotrexate, phenobarbital, & salicylate*
- Urine alkalinization is contraindicated in the case of compromised renal function or failure.
- Hypokalemia is the most common complication but can be corrected by giving K supplements.
- IV $NaHCO_3$ is used to alkalinize urine.

Urinary Excretion…

- Renal excretion of basic drugs such as *amphetamine* can be enhanced by acidification of the urine.
- Acidification can be accomplished by the admininsteration of NH_4Cl or ascorbic acid.

Dialysis

- Utility of dialysis depends on the amount of poison in the blood relative to the total-body burden.
  - If a poison has a large Vd,
  - Eg: TCAs, plasma will contain too little of the cpd for effective removal by dialysis.
  - Extensive binding of the cpd to plasma proteins impairs dialysis greatly.
  - Agents most amenable to enhanced elimination by dialysis
    - *have low molecular mass*
    - *high water solubility*
    - *low protein binding*
    - *small volumes of distribution*
    - *prolonged elimination (long half-life)*
    - *high dialysis clearance relative to total-body clearance.*
- Elimination of a toxicant by dialysis also depends on dissociation of the cpd from binding sites in tissues.

Dialysis ….

- Hemodialysis is essential in a few life-threatening intoxications, such as methanol, ethylene glycol, & salicylates.
- Passage of blood through a column of charcoal or adsorbent resin (hemoperfusion) is a technique for removal of a poison
- B/c of the high adsorptive capacity & affinity of the material in the column, some chemicals that are bound to plasma proteins can be removed.

Dialysis .....

Candidates for extracorporeal removal therapies include

- Patients with severe toxicity who deteriorate despite aggressive supportive therapy
- Those with potentially prolonged, irreversible or fatal toxicity
- Those with dangerous blood levels of toxins
- Those who lack the capacity for self-detoxification because of liver or renal failure
- Those with a serious underlying illness or complication that will adversely affect recovery.

Antagonism of an Absorbed Poison

- Once the agent responsible is suspected or identified, administration of an antidote may be necessary
- Specific chemical antagonists of a toxicant, such as
  - Opioid antagonists for opiods
  - *Atropine*: antagonist of pesticide-induced Ach excess
  - *Fomepizole:* inhibitor of ADH, for treatment of poisoning by ethylene glycol & methanol.
  - Chelating agents for metals
  - Antibodies
    - purified digoxin-specific Fab fragments of antibodies poisoning with digoxin
  - Human Monoclonal antibodies directed against specific toxins

Specific Antidotes

Mechanisms of antidote activity

- Chelation (Dimercaprol, Desferoxamine)
- Adsorption (Specific Antibodies)
- Inhibition of toxic biotransformation
  - **Fomepizole** (4-methylpyrazole)
- Enhancement of clearance by the body
- Increasing body's detoxifying capacity
  - **Na nitrite** ….to induce methemoglobin…against CN toxicity
  - **Oximes** against OPs
- Antagonism (different mechanisms of antagonism)
  - **Atropine**

Toxin-specific antidotes

Toxicant	Antidote/s
Acetaminophen	N-acetyl cysteine
Anti-cholinergics	Physostigmine
Benzodiazepenes	Flumazenil
Ca channel blockers	Glucagon, Insulin + dextrose, Calcium
Carbamate	Atropine
Cyanide	Thiosulphate, nitrate
Digoxin	Digoxin antibodies (Fab fragments)
INH	Pyridoxine
Methanol	Ethanol, Fomepizole
Glycol	Ethanol, Fomepizole
Opioid	Naloxone
Oral hypoglycaemics	Glucose
Organophosphate	Atropine, 2PAM
Warfarin	Vitamin K

Iron	Desferroxamine
Copper	Penicillamine, Dimercaprol, CaEDTA
Lead	CaEDTA, Dimercaprol (BAL)
Mercury	DMPS, DMSA, BAL
Arsenic	BAL & derivatives
Antimony	BAL & derivatives

Support & Follow-up

- Admission to ICU if necessary
- Attention to delayed and/or multi-phased toxidromes
- Psychiatric evaluation for cases of self-poisonings

Support & Follow-up…

Supportive therapy and Observation

- **IV fluids**
- **Frequent blood and urine pH adjustment**
- **Intensive nursing care**
- **Avoid unnecessary drugs**
- **Treatment for hypo- or hyperthermia**
- **Management of hypotension**

Thank you!!!